

**I. REMARKS**

Upon entry of the foregoing amendment, claims 1-7, 9-11, 13, 14, 16 and 17-21 are pending in the present application. Claims 8, 12 and 15 have been cancelled. Claims 9-11, 14 and 17-21 stand withdrawn.

Applicants have amended claims 1-3, 5 and 7 solely to advance prosecution. Applicants, by amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

It is believed this amendment does not introduce new matter and entry is respectfully requested. In this regard, applicants kindly note that claim 1 has been amended to include R2 = hydrogen in order to allow for antecedent basis in subsequent dependent claims. There is clear basis in the specification for adding R2 = hydrogen. See, for example, page 7, line 8 of the specification, as well as claim 7.

**II. REJECTION OF CLAIMS 1-7, 13 AND 16 UNDER 35 USC § 103(a)**

Beginning at page 2 of the Official Action, the Examiner has rejected claims 1-7, 13 and 16 under 35 USC § 103(a) as being unpatentable over Bauser et al. (WO 03/014116), Zhang et al. (WO 03/51877) and Niewohner et al. (WO 02/048144) in view of GB 1153670, US 4694085 and Liebig's Ann. Chem. 9, 1534-

1544 (1981).

### **RESPONSE**

The rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some motivation or teaching in the references cited by the Examiner to combine the separate elements taught in the separate references. As the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." See *KSR*

*International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

The Examiner has stated on page 3 of the Official Action that the cited references “disclose compounds that have been provided by the applicants but are very similar and do have the PDE10 activity.” The Examiner also states on page 3 that “there is a clear teaching of interchangeability of the substituents”. The Examiner goes on to state on page 4 that a person of ordinary skill “would be motivated to modify the compounds of [the cited references] to obtain the compounds of the invention...and expect them to have the same activity. Rejections based on structural similarities is [sic] founded on the expectations that compounds similar in structure will have similar properties.”

However, applicants respectfully point out that there is a key difference between the presently amended compounds claimed in this application and the compounds disclosed by the references cited by the Examiner. In particular, each of the cited references disclose compounds that require a hydrogen substitution at the 5-position of the tricyclic scaffold which corresponds to the presently claimed R5 substituent. In contrast, the presently amended claims can only have “1-4C-alkyl, 1-

4C-alkoxycarbonyl or cyano" at the 5-position of the tricyclic scaffold. Applicants have canceled the possibility of R5=H from the presently pending claims.

Applicants again note the Examiner's statement on page 4 of the Official Action that "[r]ejections based on structural similarities is [sic] founded on the expectations that compounds similar in structure will have similar properties." In order to rebut any allegation regarding a *prima facie* case of obviousness, applicants have submitted herewith a Declaration under 37 CFR §1.132 which demonstrates unexpectedly superior results. In the Declaration, similar compounds were tested wherein R5 = H was substituted for a compound that falls within the scope of currently pending claim 1.

The Declaration clearly demonstrates that the compounds as claimed in presently pending claim 1 show a totally unexpected biological profile which by no means was suggested or implied by the compounds known from the art. In particular, they show a superior pharmacological profile as PDE10 inhibiting compounds, since they unexpectedly show an increased selectivity for PDE10 over PDE4 when compared to compounds from the art where R5 is hydrogen, and for six of the nine compounds, an increased potency regarding PDE10 inhibition.

These findings are completely unexpected in view of the teachings of the prior art which merely show that compounds of formula 1 with R5 being hydrogen are capable of inhibiting PDE10. As such, a person of ordinary skill in the art would not expect that replacing hydrogen in the R5 position by alkyl, alkoxycarbonyl, or

cyano group would lead to compounds with an increased selectivity for PDE10 over PDE4, and in some respects, an increased potency regarding PDE10 inhibition.

As such, the presently rejected claims are unobvious over the cited references and withdrawal of this rejection is respectfully requested.

### **III. REJECTION OF CLAIMS 1-7, 13 AND 16 UNDER 35 USC § 103(a)**

Beginning at page 5 of the Official Action, the Examiner has rejected claims 1-7, 13 and 16 under 35 USC § 103(a) as being unpatentable over "Casandra et al." Applicants respectfully note that no "Casandra et al." reference has ever been cited by applicants or the Examiner. Applicants assume that the Examiner intended to recite "Casagrande et al." which was cited by the Examiner as reference "V" on the Notice of References cited and attached to the Official Action.

### **RESPONSE**

The rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

Relevant authority regarding the requirements that the Examiner must meet to establish a *prima facie* case of obviousness is outlined in Section II above.

Similar to each of the cited references that were discussed in Section II, the Casagrande et al. reference also does not disclose compounds with any substituent at the 5-position of the tricyclic scaffold other than hydrogen.

In contrast, the presently amended claims can only have "1-4C-alkyl, 1-4C-alkoxycarbonyl or cyano" at the 5-position of the tricyclic scaffold. Applicants have canceled the possibility of R5=H from the presently pending claims.

As such, applicants again refer to the unexpectedly superior results of the presently claimed compounds over those disclosed by the prior art as discussed in Section II and demonstrated in the attached Declaration. In particular, applicants respectfully submit that a person of ordinary skill in the art would not expect that replacing hydrogen in the R5 position by alkyl, alkoxycarbonyl, or cyano group would lead to compounds with an increased selectivity for PDE10 over PDE4, and in some respects, an increased potency regarding PDE10 inhibition.

Therefore, it is respectfully submitted that Casagrande et al. cannot render the presently pending claims obvious in view of the clear structural differences between the disclosed compounds and the presently claimed compounds. Further, any alleged finding of a *prima facie* case of obviousness is moot in view of the data presented herein which clearly shows that the presently claimed subject matter is unexpectedly superior over the compounds of the prior art.

As such, the presently rejected claims are unobvious over the cited references and withdrawal of this rejection is respectfully requested.

#### **IV. REJECTION OF CLAIMS 1-7 AND 11 UNDER 35 USC § 103(a)**

Beginning at page 7 of the Official Action, the Examiner has rejected claims

1-7 and 11 under 35 USC § 103(a) as being unpatentable over Anderson et al.

### **RESPONSE**

The rejection is respectfully traversed. The Examiner has not established a *prima facie* case of obviousness against the presently pending claims.

Relevant authority regarding the requirements that the Examiner must meet to establish a *prima facie* case of obviousness is outlined in Section II above.

Similar to each of the cited references that were discussed in Section II, the Anderson et al. reference also does not teach the presently amended compounds which contain substituents at the 5-position of the tricyclic scaffold other than hydrogen.

In fact, the presently amended claims can only have "1-4C-alkyl, 1-4C-alkoxycarbonyl or cyano" at the 5-position of the tricyclic scaffold. Applicants have canceled the possibility of R5=H from the presently pending claims.

As such, applicants again refer to the unexpectedly superior results of the presently claimed compounds over those disclosed by the prior art as discussed in Section II and demonstrated in the attached Declaration. In particular, applicants respectfully submit that a person of ordinary skill in the art would not expect that replacing hydrogen in the R5 position by alkyl, alkoxycarbonyl, or cyano group would lead to compounds with an increased selectivity for PDE10 over PDE4, and in some respects, an increased potency regarding PDE10 inhibition.

Therefore, it is respectfully submitted that Anderson et al. cannot render the presently pending claims obvious in view of the clear structural differences between the disclosed compounds and the presently claimed compounds. Further, any alleged finding of a *prima facie* case of obviousness is moot in view of the data presented herein which clearly shows that the presently claimed subject matter is unexpectedly superior over the compounds of the prior art.

As such, the presently rejected claims are unobvious over the cited references and withdrawal of this rejection is respectfully requested.

**V. REJECTION OF CLAIMS 1-7, 11 AND 13 UNDER 35 USC § 112, 1<sup>ST</sup> PARAGRAPH**

At page 9 of the Official Action, the Examiner has rejected claims 1-7, 11 and 13 under 35 USC § 112, 1<sup>st</sup> paragraph as being non-enabled.

**RESPONSE**

The rejection is respectfully traversed. However, solely to advance the prosecution of this application, applicants have presented amendments herein to the rejected claims.

In this regard, applicants note the Examiner's statement on page 9 that "the specification, while being enabling for substituents to be H, alkyl, alkoxy carbonyl alkyl, cyano, does not reasonably provide enablement for all the various substituents."



Regarding the Examiner's statement about the enablement of the various substituents presently claimed, it is not entirely clear what the Examiner's statement means. Is the Examiner suggesting that all substituents are enabled for H, alkyl, alkoxy carbonyl alkyl and cyano even for those substituents that do not presently claim them? Is the Examiner suggesting that, only where these substituents are claimed, they are enabled? Is the Examiner suggesting that only these four substituents are enabled, even where the application clearly indicates that compounds have been actually synthesized that have substituents other than these four?

In any event, applicants respectfully submit that there are many more substituents presently claimed that are clearly enabled by the present specification in addition to those alleged are enabled by the Examiner. At a minimum, such compounds have been synthesized and/or there is clear direction on how to synthesize them, and should accordingly be viewed as enabled. See, for example, Table 1 on pages 14-15, Tables A1-A4 on pages 18-20 and Tables B1-B4 on pages 20-23, and Examples 1-69 on pages 28-35 of the present specification.

Applicants remind the Examiner that working examples, while not required to demonstrate enablement, are clear indicators of enablement, where present. The Examiner, however, on page 11 of the Official Action has erroneously stated that "the instant specification does not have any working examples". In contrast to the

Examiner's erroneous statement, there are no fewer than 139 example compounds that have been synthesized.

Moreover, the Examiner has also stated at page 11 that "the inventor provides very little direction in the instant application". Applicants disagree with the Examiner's position regarding the amount of direction provided. The instant specification contains sufficient direction that would enable the ordinary skilled artisan to synthesize the presently claimed compounds. See the reaction schemes and other disclosure at pages 23-27 of the present specification.

Further, the Examiner has indicated on page 11 in her Wands factors analysis that "the state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities". Applicants respectfully submit that all method claims 9, 14 and 17-21 have been withdrawn as being directed to non-elected subject matter. It is not necessarily appropriate for the Examiner to now rely on allegations as to what is known in the "state of the prior art" regarding non-elected subject matter. Applicants respectfully submit that the Examiner should instead focus on the elected subject matter, i.e. the compound claims.

Regarding the Examiner's statements on page 10 that "synthesizing compounds is very difficult" (see section 3) and "the pharmaceutical art is unpredictable" (see section 5), applicants submit that the Examiner has also conceded that the ordinary artisan in the pharmaceutical arts is "highly skilled" (see

section 4). Based on the disclosure contained in the application as a whole, applicants respectfully submit that the amount of experimentation that may be required by the highly skilled person in the pharmaceutical arts to synthesize the presently claimed compounds is not undue.

Accordingly, applicants submit that the presently pending claims are clearly enabled by the instant specification. As such, reconsideration and withdrawal of this rejection is respectfully requested.

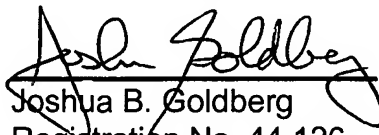
**VI. CONCLUSION**

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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